REMARKS

The Claim Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 14-21, 30 and 33 and have canceled claims 2, 4-13, 22-29, and 31-32. Specifically, claim 1 has been amended to recite a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a complementary sense strand and an antisense strand, wherein: each strand of said siRNA molecule is about 18 to about 27 nucleotides in length; the antisense strand of said siRNA molecule comprises about 18 to about 27 nucleotides that are complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to SEQ ID NO:474; the sense strand of said siRNA molecule comprises a portion of said VEGF nucleotide sequence of about 18 to about 27 nucleotides; and said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide.

Support for the amendments to claim 1 can be found, inter alia, at pages 7-12 (chemically modified siRNA, sense strand and antisense strand, antisense strand complementarity to VEGF sequence, sense strand comprising a portion of VEGF sequence); pages 16, 20, and 29-30 (2'-O-methyl and 2'-deoxy-2'-fluoro modifications); page 36 (about 18 to about 27 nucleotides in length); and pages 7, 8, 9, 11, 56, 75, and 150, and 155-165 (referring to GenBank Accession No. NM_003376, SEQ ID NO:474). Claim 1 and dependent claims 3, 14-21, 30 and 33 have been amended to recite the term "siRNA" rather than "siNA". Support for these amendments can be found, inter alia, at pages 1, 7, 11, 70 and throughout the specification. Claims 14-16, 18-21, and 30 have been amended to recite the term "strand" instead of "region". Support for these amendments can be found, inter alia, at pages 11, 12, 17, 23-26, 28-35 and throughout the application. Claims 14, 15, and 18-20 have been amended to recite the term "one or more". Support for these amendments can be found, inter alia, at pages 19-21, 24, 27,

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CERTIFICATE OF MAILING UNDER 37 CFR § 1.10

The undersigned hereby certifies that this Transmittal Letter and the papers, as described in paragraph 1, are being deposited with the United States Postal Service under Express Mail Label No. EV839383339US in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 21, 2006.

Anita J. Terpstra, PhD.

and 29-30. Claim 30 has been amended to recite the term "terminal" with regard to the claimed phosphate group. Support for this amendment can be found, inter alia, at page 32. Claim 69 has been amended to recite the term "pharmaceutically acceptable carrier or diluent". Support for the amendment can be found, inter alia, at pages 58 and 110.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO: 474. The sequence represents GenBank entry NM_003376 (see Tables I and II). Applicant submits that the CD-R submitted in lieu of the paper copy and the CD-R submitted for the computer-readable copy are identical in content. The sequence listing adds no new matter and applicants respectfully request its entry.

Priority

The Office Action alleges that the instant application is not entitled to a priority date earlier than September 16, 2003, which is the filing date of USSN 10/665,255 because support for the terms "about 19 to about 21 base pairs" or "about 21 nucleotides" is not found in any of the later filed parent applications (see Office Action at page 3). The Applicant respectfully disagrees with the Office's assessment of the priority claim because the instant application claims priority, *inter alia*, to U.S. provisional patent application Nos. 60/363,124 (the '124 application) and 60/358,580 (the '580 application). The claims presented above all find complete support in the '124 and '580 applications.

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In particular, amended claim 1 finds support for chemically modified double stranded siRNA at page 3, lines 15-17; page 6, lines 19-24; and page 24, lines 22-24 of the '124 application and pages 3, 5, and 20-21 of the '580 application; comprising a sense strand and an antisense strand at page 7, lines 9-11 of the '124 application and pages 6-7 of the '580 application; each strand is about 18 to about 27 nucleotides in length at page 12, lines 4-12 of the '124 application and page 11 of the '580 application; complementarity between the sense and antisense strands at page 12, lines 4-7, and page 25, lines 17-29 of the '124 application and pages 11, 21-22 of the '580 application; the antisense strand having between 18-27 nucleotides complementary to VEGF nucleotide sequence corresponding to SEQ ID NO:474 at page 18, lines 1-5 and page 389 for GenBank Accession No. NM_003376 of the '124 application; sense strand comprising a portion of HCV sequence at page 15, lines 17-19 and 30-31 of the '124 application and page 15 of the '580 application; and 2'-O-methyl or 2'-deoxy-2'-fluoro modifications at page 5, lines 13-22; page 6, line 19 to page 7, line 18 (where R3 of Formula II is F or O-alkyl); and pages 10-11 of the '124 application and pages 5, 6, 7, 10, and 11 of the '580 application.

Support for the dependent claims can also be found, *inter alia*, in the '124 and '580 applications:

Claim	Support
3	One or more ribonucleotides: p. 15, lines 3-9 ('124); p. 14 ('580)
14	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 19-23 ('124); p. 5-6 ('580)
15	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 11-13 ('124); p. 10 ('580)
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18 ('124); p. 8-9 ('580)
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18 ('124); p. 5, 14, and 35 ('580)
18	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 11-13 ('124); p. 10

Claim	Support
	('580)
19	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 19-25 ('124); p. 5-6 ('580)
20	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 19-23; p. 5-6 ('580)
21	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25 ('124); p. 9 ('580)
30	Terminal phosphate group: p. 8, line 26 to p. 9, line 13 ('124); p. 8-9 ('580)
33	Composition comprising the double stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19 ('124); p. 16-17 ('580)

Support for all of the pending claims can be found in the '124 and '580 applications. The instant application claims priority to and incorporates by reference PCT/US03/05043 in its entirety, which application claims priority to and incorporates by reference, inter alia, the '124 and '580 applications in their entirety. Thus, the instant application properly claims priority to the 60/363,124 and 60/358,580 applications. Applicant respectfully submits that the instant invention is entitled to a priority date of at least February 20, 2002.

Claim Objections

Claim 18 was objected to because it was missing a period at the end of the claim. Accordingly, Claim 18 has been amended to add a period to the claim, thus obviating the objection.

Claim 31 was objected to because of a typographical error due to a misspelling of the word "comprises" as "comprisess" appearing in the claim. Claim 31 has canceled, thus obviating the objection.

Obviousness-Type Double Patenting Rejection

Claims 1-33 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1-30 of copending Application No. US Publication No. 20040209832.

Without acceding to the merits of the rejection, Applicant will consider filing a terminal disclaimer upon allowance of the pending claims.

35 U.S.C. § 112 Rejection

Claims 1-33 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 2, 4-13, 22-29, and 31-32 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 14-21, 30 and 33.

The Office Action asserts that although the specification as filed discloses numerous siNA sequences targeted to VEGF, the specification does not provide information regarding what structure targets any VEGF RNA via RNAi other than siNAs targeting GenBank Accession Number NM_003376. The Office Action concludes that the skilled artisan would not be able to envisage the entire genus of siNA molecules that would direct cleavage of any VEGF RNA other than siNAs targeting GenBank Accession Number NM_003376.

Applicants respectfully disagree with this argument because the specification teaches how to design, synthesize, and test siNA molecules targeting any VEGF target sequence and provides numerous examples of other VEGF RNA target sequences via GenBank Accession numbers listed on pages 150-153 of the instant specification. However, in the interest of expediting prosecution, claim 1 has been amended and is now directed to a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a complementary sense strand and an antisense strand, wherein: each strand of said siRNA molecule is about 18 to about 27 nucleotides in length; the antisense strand of said siRNA molecule comprises about 18 to about 27 nucleotides that are complementary to a vascular endothelial growth factor (VEGF)

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nucleotide sequence corresponding to SEQ ID NO:474 (NM_003376); the sense strand of said siRNA molecule comprises a portion of said VEGF nucleotide sequence of about 18 to about 27 nucleotides; and said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. The claim as amended is fully supported by the written description of the application and priority documents as discussed in detail above under the discussion of priority. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

35 U.S.C. § 102 Rejections

Claims 1, 3-9, 23, and 31-33 were rejected under 35 U.S.C. 102(a) as being anticipated by Reich *et al.* (Molecular Vision, 2003 Vol. 9, pages 210-216). Claims 4-9, 23, and 31-32 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3 and 33.

Applicant believes that the presently claimed invention has an effective filing date of February 20, 2002 (see priority discussion above) which precedes Reich *et al.* Thus, Applicant believes that Reich *et al.* is not a proper prior art reference. Furthermore, even if Reich *et al.* were considered to be prior art, it does not teach the presently claimed invention. The siRNA molecules described in Reich *et al.* are not chemically modified with 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides as are the presently claimed siRNA molecules. Given that Reich *et al.* do not teach each and every element of the claimed invention, it does not anticipate. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §102(a) rejection.

35 U.S.C. § 103 Rejections

Claims 1-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Reich *et al.* (Molecular Vision, 2003 Vol. 9, pages 210-216), in view of Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888), Cook *et al.* (U.S. Patent No. 5, 587,471), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, pages 573-581). Claims 2, 4-13, 22-29, and 31-32 have been canceled. Therefore, the rejection is moot as applied to these

claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 14-21, 30 and 33.

As described above, Applicants submit that Reich *et al.* is not prior art to the instantly claimed invention because Reich et al. was published after the effective filing date of the instantly claimed invention. This alone is sufficient to obviate the present 35 U.S.C. 103(a) rejection.

However, even considering the teachings of Reich *et al.,* Applicants submit that the Office Action has still not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the presently claimed invention. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art

references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Initially, Applicant notes that with respect to Cook et al. and Schmidt et al., the Office cites Cook et al for teaching glyceryl modifications and Schmidt et al for teaching hairpin nucleic acid inhibitors comprising sense and antisense regions that are connected via a polynucleotide or non-polynucleotide linker. Applicant points out that claims 9-12 (directed to sense and antisense regions connected via a linker) and claim 22 (directed to a siRNA molecules having a glyceryl odification) have been canceled.

Furthermore, Applicant submits that one of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Reich *et al.* provides no teaching whatsoever with respect to modified siRNA molecules. With respect to the other references, Elbashir is the only reference cited that teaches a general structure of the claimed nucleic acid molecules, i.e., a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. All of the other references describe either long double stranded RNA (Parrish), antisense (Cook *et al.*) or ribozyme art (Schmidt *et al.*). Although long double stranded RNA, antisense, and ribozymes are nucleic acid based technologies, they differ substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification

strategies that allow such molecules to remain active. Just as ribozyme and antisense modifications are not amenable to long double stranded RNA and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs as described by Elbashir.

The Office Action states that "One of ordinary skill in the art would have a reasonable expectation of success of making a modified double-stranded siNA molecule that down-regulates expression of a VEGF gene given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides, such as increasing resistance to nucleases" (see Office Action at page 14). However, as described in detail below, the prior art provides insufficient basis for the ordinary artisan to have had a reasonable expectation that the modified double stranded RNA molecules taught in the art would have the properties of effectively inducing RNAi, and, indeed, the prior art teaches away from the claimed chemically modified siRNA molecules.

The Office Action states that "Parrish *et al.* teach 2'-deoxy'2-fluoro pyrimidine modifications in the sense or antisense strand" (see Figure 5). However, the Parrish *et al.* reference does not teach modified siRNA, as all of the modified constructs tested by Parrish *et al.* were long double stranded RNAs (as described below) that were prepared using enzymatic methods. The paper by Parrish represents a broad survey of the biochemical properties of the RNAi reaction in nematodes using long dsRNAs, but it does not provide any useful information regarding the design of modified siRNA molecules, including chemically modified siRNA. In 2000–2001 it was clear that RNAi was a conserved cellular mechanism that was present in a diverse set of organisms; it was first discovered in plants, then in nematodes, ciliates, fungi, Drosophila, and finally in mammalian cells (see for example Elbashir *et al*). But while the basic mechanism is conserved, it was clear to those skilled in the art that the mechanistic details could be very different from one organism to another, as is evidenced by publications at the time. Specifically, the lower Eukaryotes are easily activated by long dsRNA, while publications such as Elbashir *et al.*, 2001, EMBO J., Vol 20, No. 23, pages 6877-6888,

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noted that long dsRNA failed to stimulate RNAi in mammalian cells; this was likely due to the activation of an interferon response in mammalian cells, which is absent in the lower Eukaryotes. Likewise, Bernstein *et al* (2001, *RNA* **7**:1509-1521) noted that *C. elegans* and plants have a number of RNAi-related behaviors that are not found in mammalian cells, including the ability to pass the RNAi effect from one cell to the next, the ability to amplify the RNAi response such that a few dsRNA molecules can elicit a potent RNAi response, and the ability to pass the RNAi response from one cell generation to the next due to the long-lived nature of RNAi in these organisms (p1515-1516). These profound differences would teach those skilled in the art that it is unwise to generalize discoveries made in *C. elegans* to the world of mammalian RNAi.

A second factor that makes it difficult to draw lessons from Parrish *et al.* is that all of the studies were performed using long dsRNA. The shortest dsRNA molecules used were 26 & 27 bp, but these were only used for initial base composition studies and not for chemical modification studies. In fact, Parrish clearly states that any molecules less than 26 bps were inactive (p1079, right column). The nucleotide modification studies were performed primarily using a 742 bp *unc*-22A sequence that apparently also contained "3–30 nt of dsRNA derived from polylinker sequences on each end, and polylinker-derived single stranded tails of 10–30 nt." (Materials & Methods, p1085). The authors checked the annealing of these sequences by agarose gel, but that would only confirm that they were stuck together, not whether they were annealed properly. These long sequences add a great deal of ambiguity to the interpretation of the results. An "inactive" modification could be such because it failed to allow the strands to anneal properly rather than being deleterious to the RNAi machinery, and an "active" modification could actually be an inactive modification that is distributed sparsely enough on the sequence that the RNAi machinery can still function. This latter possibility is of particular concern since Parrish reports that they "were able to demonstrate interference activity following incorporation of any single modified residue", but that "RNAs with two modified bases also had substantial decreases in effectiveness as RNAi triggers." (p1081, right column). Thus, the modifications have a cumulative effect such as would be expected if the RNAi machinery was finding unmodified places on the long dsRNA to bind and activate.

One final argument against Parrish is that they themselves were unable to formulate a cogent conclusion to their chemical modification studies. They tested over 30 combinations of chemical modifications (their Figure 5, Figure 6, and data not shown), but in the discussion section they can only muster three short paragraphs speculating on the possible implications of these studies (p1084, left column). Their conclusions are: (1) the dsRNA might need to maintain an A-form helix to be active, (2) the antisense strand is more sensitive to modification than the sense strand, and (3) some modifications affect RNAi activity when added to either strand. These speculations are only weakly supported by the data. Coupled with the concerns mentioned above regarding long dsRNA and the difficulty of extending observations from *C. elegans* to mammalian cells, these considerations would have made it very difficult for one of skill in the art to draw any conclusions whatsoever from Parrish regarding the design of short siRNA molecules.

Furthermore, the knowledge of one of ordinary skill and the state of the art at the time of filing the present application prevented the siRNA molecules claimed in the instant application from being realized. As demonstrated by Elbashir *et al*, the results of testing of chemically modified *short double stranded RNA* clearly teach away from the present invention. Elbashir attempted to apply chemical modifications to siRNA based on the teachings of the prior art, including Parrish (see for example Elbashir *et al.*, 2001, Genes and Development, 15:188-200, and which references the work of Parrish at page 198), but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion on pages 6881 and 6882 of Elbashir describes siRNA duplexes having internal base paired modifications (2'-deoxy and 2'-O-methyl) and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced

> by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where substantial internal base paired substitutions were used, such modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbahsir,

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

It is important to understand that because the first sentence quoted above references only 2'-deoxy modifications and not 2'-O-methyl modifications, the term "More extensive" in the second sentence can modify only "2'-deoxy" in the second sentence and not "2-O-methyl." The beginning of the second sentence is equivalent to "2'-O-methyl and more extensive 2'-deoxy modifications reduce the ability of siRNAs to mediate RNAi." Thus, Elbashir flatly states that 2'-O-methyl modifications should be avoided.

The Office action states that "It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the siNA...since the prior art taught such modifictions protect the nucleic acid molecule from nuclease degradation" (see Office Action at page 13). However, based on the teachings of "[t]he siRNA Users Guide" from Elbashir, one of skill in the art would have avoided making any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not have been motivated to pursue the presently claimed invention, *i.e.*, a chemically modified siRNA molecule having at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. How could one have been motivated to make more extensive modifications when the **only** piece of prior art dealing directly with short double stranded RNA molecules expressly states that more extensive modifications result in decreased activity?

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This conclusion is further supported by publications in the field in the 2001 and 2002 time frame, where experts in the field followed the teachings of Elbashir *et al.*, 2001, EMBO J. Vol. 20, No. 23, pages 6877-6888 and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; and Holen *et al.,* 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references demonstrate that Elbashir taught away from the presently claimed invention and not just from 100% modified duplexes. If it would have been obvious, clearly, the presently claimed invention would have been practiced by those of skill in the art, including Elbashir and those that followed Elbashir's teaching.

The above argument is best explained by a plain reading of Elbashir, which teaches that no modifications other than 3'-terminal deoxy nucleotides are not tolerated and likely interfere with protein association in siRNP assembly. As such, Elbashir did not provide any motivation to a person skilled in the art to take the teachings of the prior art, e.g., long dsRNA, antisense or ribozymes, and apply it to short double stranded RNA molecules as presently claimed because Elbashir tried this approach and failed; Elbashir therefore teaches away from using modifications beyond use of 2'-deoxynucleotides at the 3'-terminal positions of the short double stranded RNA molecules and not just 100% modification. One of skill in the art would not have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2'-fluoro modifications within a siRNA molecule as is presently claimed.

The cited references, alone or in combination, do not provide a reasonable expectation of success, as is clearly shown from the teachings of Elbashir and the state of the art following Elbashir. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is

irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, one can not use the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000).

Applicant submits that no *prima facie* case of obviousness exists because, as described above, Reich et al. is not prior art to the present invention, and furthermore there would have been no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach against the instant claims. Because no prima facie case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims.

The applicants are the first ones to show that selective incorporation of 2'-O-methyl and 2'-deoxy-2'-fluoro modifications are well tolerated in siRNA molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully down regulate gene expression. For example, in the instant application USSN 10/764,957, published as US-2005-0054596-A1, Applicant has designed, synthesized, and tested the presently claimed 2'-deoxy-2'-fluoro and 2'-O-methyl modified siRNA molecules having potent activity directed against VEGF gene expression (see for example Figure 14 and corresponding descriptions on pages 90 and 138). In addition, in co-pending application USSN 10/444,853, published as US-2004-0192626, applicant has designed, synthesized, and tested several 2'-deoxy-2'-fluoro and 2'-O-methyl modified siRNA molecules having potent activity directed against several different gene targets (see for example Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-

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15). These co-pending applications demonstrate that application of 2'-deoxy-2'-fluoro and 2'-O-methyl modifications to siRNA structures are well tolerated for maintaining potent RNAi activity against VEGF and other target nucleic acid sequences.

For the reasons set forth above, Reich et al. is not prior art to the present invention. Furthermore, a person skilled in the art would not have been motivated to follow the teachings of Elbashir, let alone Parrish or the antisense and ribozyme art, to make and use the double stranded nucleic acid molecules of the present invention to target human VEGF gene expression. Thus, Reich *et al.* (Molecular Vision, 2003 Vol. 9, pages 210-216), in view of Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888), Cook *et al.* (U.S. Patent No. 5, 587,471), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, pages 573-581), alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
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Date: June 21, 2006

By: _____
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